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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Method of Enhancing the Activity of Parentally Administrable Drugs

We, LABORATORIE DE RECHERCHES PHYSIQUES S.a.r.l., a body corporate organised under the laws of Switzerland, of Villa Marguerite, Veyrier, Geneva, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the use of certain chemical compounds for potentiating certain parentally administratable drugs.

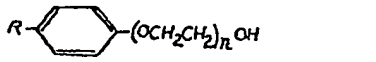
It is well known that many drugs act in the human or animal body at certain active sites, usually at the surface of nerve tissue, which sites are protected by a complex lipid barrier through which the drug must pass before any physiological action occurs. Drugs which act in this way are hereinafter referred to as "of the type described".

Experiments have shown that with this type of drug a substantial amount of the drug is absorbed by the lipid barrier layer and never reaches the active site. Thus a large excess of drug is required to ensure that sufficient drug passes through the lip barrier layer to bring about the desired physiological effect. This is necessarily wasteful since a considerable quantity of the drug is absorbed by the lipid barrier layer and is eventually excreted or otherwise destroyed by the body processes without it ever reaching the active site.

In accordance with the present invention it has been found that this problem of drug retention by the lipid barrier layer in warm blooded animals can be mitigated if there is injected into the animal body a non-toxic surface active agent which is injected either at the same time as the drug or shortly before or afterwards so that it is present in the body during the period of drug activity. By this means absorption of the drug by the lipid barrier layer is reduced thereby increasing the amount of drug available at the active site. Thus the dosage rate can be considerably reduced.

In one aspect, therefore, the present invention is a method of enhancing the activity of parenterally administratable drugs of the type described, and in a second aspect is a parenterally administrable composition comprising a liquid carrier, a drug of the type described and a surface active agent.

The surface-active agents used in this invention may, in general, be any non-toxic surface active compound capable of parenteral administration. Preferred surface active agents are quaternary ammonium compounds, sulfosuccinates, polyoxyethylene condensates of long chain alkanols and sulfuric acid monoesters thereof, alkylated phenoxyethanols and alkylated phenoxy (polyethanols). Particularly prefered surface active agents used in this invention are compounds of the formula:



where R is a C_1—C_{18} alkyl radical and n has an average value of from 1—30, inclusive. Typical compounds of this group are those where R is nonyl or octyl and n=6 or from 9 to 10, respectively, or where R is $(CH_3)_3C$—CH_2—$C(CH_3)_2$— and n is from 9 to 10.

The drugs which may be potentiated in accordance with this invention cover a very wide range. Typical of such drugs are stimulants such as adrenaline, nor-adrenaline and digitoxin, blocking agents such as lidocaine and the various forms of curare, and vasoconstrictors such as serotonin.

In general, the amount of surface active agent employed in the method and in the

[*Price* 4*s.* 6*d.*]

compositions of this invention may vary over a wide range. Generally, however, it will be administered or be present in the compositions in an amount of from 0.1—10% by weight based on the weight of the drug.

The degree of drug activity enhancement achieved by the present invention can be quite remarkable, for instance, the physiological effects of a drug such as adrenaline may be potentiated by as much as 100% over the normal control value by the use of or practice of this invention. Thus, with the invention it is possible to use lesser amounts of a given drug for a particular stated purpose and still achieve the same effect quantitatively as regards order of magnitude of response that would normally be achieved when the drug is used alone, i.e., in the absence of surfactant. For example, normal drug doses in the case of the representative compounds previously mentioned have been reduced by as much as 90% to gain the same response normally achieved when the drug is used alone at the aforementioned higher level.

In carrying out the process of this invention, the surface active agent can be administered either before or after the parenteral administration of the drug itself provided that the interval between the two is not too great, i.e. not generally in excess of about fifteen minutes. However, it is preferred in practice to administer the surface active agent and the drug together simultaneously in a common carrier.

For purposes of simultaneous parenteral administration, the drug and the surface active agent can be combined in a common carrier such as in sesame oil, peanut oil, aqueous-propylene glycol or N,N-dimethylformamide. Alternatively, the two components can be administered in a sterile aqueous solution. Such aqueous solutions should be suitably buffered, if necessary, and the liquid carrier first rendered isotonic with sufficient saline or glucose. These solutions are particularly valuable for intravenous, intramuscular and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are readily obtained by standard techniques well known to those skilled in the art. For instance, when distilled water is ordinarily used as the liquid carrier, the final preparation can be passed through a suitable bacterial filter, such as a sintered glass filter. Preferred filters of this type include the Berkefeld (Registered Trade Mark), the Chamberland and the asbestos disc-metal Seitz filter, wherein the fluid is sucked through the filter candle into a sterile container with the aid of a suction pump. Needless to say, aseptic conditions must necessarily be maintained throughout all these operations which are directlty connected with the preparation of the aforesaid injectable solutions.

This invention is further illustrated by the following examples, all parts and percentages are by weight.

Example I

An anesthetized dog was rigged for registration of heart-rate and respiration in the standard way and cannulated for ready injection of various parenteral solutions. When the animal registered a steady state, adrenaline in a 0.1% solution (in oil) was administered *via* this route at the 0.2—0.6 ml. dose level, i.e., a threshold concentration, and readings were thereafter taken with respect to the amplitude and persistance of response of said animal, as well as to its recovery with time. After final recovery, a dose of the same drug was prepared having only one-tenth the concentration of the aforesaid test dose. This was then mixed with 2 ml. of 0.01% Triton X-100 in Ringer (saline) solution, and the resulting mixture was injected into the same animal as before *via* the cannula (Triton X-100 is a Registered Trade Mark and is a surface active agent of the formula $(CH_3)_3C—CH_2—C(CH_3)_2—C_6H_4(OCH_2CH_2)_{9-10}OH$). The results obtained in this manner are such that the dose response effect which is produced in the case of the Triton-containing solution at least equals that which is caused by the more concentrated adrenaline solution lacking the surfactant agent. Further tests also established that the animal shows no real response to the Triton X-100 when employed at this concentration alone in Ringer solution.

Example II

The procedure described in Example I was repeated with an isolated frog heart. The heart was mounted for Ringer solution perfusion with a "T" in the line so as to facilitate side-tube introduction of the drug as well as large scale (volume) washing of the system. Otherwise, the experimental routine or test procedure is essentially the same as in Example I. In like manner, the dose-response results obtained with adrenaline in the present case are also substantially the same, i.e., the effect produced by the Triton surfactant on the drug is of substantially the same order of magnitude as that reported in Example I.

Example III

Adrenaline was injected into the isolated heart as in accordance with the procedure of Example II, but lacking the added Triton X-100 at this point. After normal response and full recovery, followed by a multiple-washing, a small quantity (2 ml.) of Triton X-100 in Ringer solution at the 0.01%, concentration level was injected into the so-treated organ without any drug. It was observed that the heart immediately responded with the same reaction that the adrenaline gave in the first instance, thereby indicating

that a large unused portion of the drug had still been present in the isolated, washed organ (not doubt, bound in the lipid barrier) prior to the administration of the surfactant.

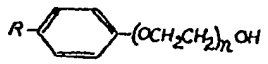
In like manner, substantially the same results were also achieved with the intact dog when the above procedure was repeated using this particular animal instead of the aforesaid isolated organ.

EXAMPLE IV

The procedure described in Example I is repeated in dogs using other compounds in place of adrenaline. Thus, for instance, the following compounds have been used on an individual basis: nor-adrenaline, tube or bamboo curare, pot curare and gourd or calabash curare, lidocaine, serotonin and digitoxin. In each case, the results obtained are substantially the same as those reported previously for adrenaline in Example I.

EXAMPLE V

The procedure of Example I is followed except that other surface-active agents are employed in place of Triton X-100 and these are listed below as follows:



R	n	R	n
CH_3	1	C_9H_{19}	1.5
CH_3	30	C_9H_{19}	4
iso-C_3H_7	5	C_9H_{19}	6
tert.-C_4H_9	18	C_9H_{19}	9
n-C_6H_{13}	6	C_9H_{19}	9—10
$(CH_3)_3C—CH_2—C(CH_3)_2$	1	C_9H_{19}	10—11
$(CH_3)_3C—CH_2—C(CH_3)_2$	3	C_9H_{19}	15
$(CH_3)_3C—CH_2—C(CH_3)_2$	5	C_9H_{19}	20
$(CH_3)_3C—CH_2—C(CH_3)_2$	7— 8	C_9H_{19}	30
$(CH_3)_3C—CH_2—C(CH_3)_2$	12—13	$C_{12}H_{21}$	15
$(CH_3)_3C—CH_2—C(CH_3)_2$	16	$C_{16}H_{29}$	9
$(CH_3)_3C—CH_2—C(CH_3)_2$	20	$C_{16}H_{33}$	1
$(CH_3)_3C—CH_2—C(CH_3)_2$	30	$C_{16}H_{32}$	30

In each and every case, the results obtained are substantially the same as those reported previously in Example I.

EXAMPLE VI

The procedure of Example I was repeated using other animal species in place of the dog. Among the animals that have been specifically tested in this manner are the cat, rabbit, frog and electric eel, with the results obtained in each case being substantially comparable to those obtained with the dog.

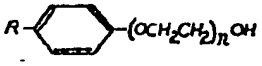
EXAMPLE VII

The procedure described in Example II was repeated using other isolated organs in place of that of the frog's heart. Among the organs specifically tested in this manner are the hearts of dogs and eels, as well as muscle and nerve preparations taken from all three species of animals. In each and every case, the results obtained are substantially identical with those for the frog heart.

The treatment of human beings is hereby disclaimed. Subject to this disclaimer what we claim is:—

1. A sterile composition for parenteral administration comprising a liquid carrier, a parenterally administrable drug of the type described and from 0.1—10% by weight based on the weight of the drug of a non-toxic surface active agent selected from the following: quaternary ammonium compounds, sulfosuccinates, polyoxyethylene condensates of long chain alkanols, or sulfuric acid monoesters thereof, alkylated phenoxyethanols or alkylated phenoxy (polyethanol)s.

2. A composition according to Claim 1, in which the surface active agent is of the formula



where R is C_1—C_{18} alkyl and n has an average value of from 1—30.

3. A composition according to Claim 2, where R in said formula is nonyl or octyl and n is 6 or from 9 to 10 respectively.

4. A composition according to Claim 3, where R in said formula is $(CH_3)_3C—CH_2—C(CH_3)_2$— and n is from 9 to 10.

5. A composition according to any one of the preceding claims, in which the drug is adrenaline, nor-adrenaline, curare, lidocaine, serotonin or digitoxin.

6. A composition according to any one of the preceding claims, in which the liquid carrier is sesame or peanut oil, aqueous propylene glycol or N,N-dimethylformamide.

7. A composition according to any one of Claims 1—5, in which the carrier is a buffered isotonic aqueous solution.

8. A method of enhancing the activity of parenterally administrable drugs of the type described in warm blooded animals, which comprises parenterally administering to the animal a non-toxic surface active agent, the surface active agent being administered simultaneously with, shortly before or shortly after said drug so as to be present in the animal body during the period of activity of the drug.

9. A method according to Claim 8, wherein the surface active agent is selected from the group specified in Claim 1.

10. A method according to Claim 8, wherein the surface active agent is as specified in Claims 2, 3 or 4.

11. A method according to Claims 8, 9 or 10 wherein the drug is any one of those specified in Claim 5.

12. A method according to any one of Claims 8—11, wherein the drug and the surface active agent are administered simultaneously in a common carrier.

13. A method according to Claim 12, wherein the drug and the surface active agent are administered simultaneously in the form of a composition as claimed in any one of Claims 1—7.

For the Applicant
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